AD_____

Award Number: W81XWH-10-1-0532

TITLE: Vitamin D Levels and Related Genetic Polymorphisms, Sun Exposure, Skin Color, and Risk of Aggressive Prostate Cancer

PRINCIPAL INVESTIGATOR: Adam B. Murphy, MD, MBA

CONTRACTING ORGANIZATION:
NORTHWESTERN UNIVERSITY
EVANSTON IL 60208-0001

REPORT DATE: July 2012

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-07-2012	Annual Summary	1 JUL 2011 - 30 JUN 2012

4. TITLE AND SUBTITLE

Vitamin D Levels and Related Genetic Polymorphisms, Sun Exposure, Skin Color, and Risk of Aggressive Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0532

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Adam B. Murphy

E-Mail: a-murphy2@northwestern.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

NORTHWESTERN UNIVERSITY
EVANSTON IL 60208-0001

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Data from epidemiologic reports have had mixed results on the role of vitamin D deficiency as a risk factor for prostate cancer incidence and aggressiveness. The prior studies often failed to control adequately for season, skin color, sun exposure, genetic polymorphisms or the other biological and environmental mediators of vitamin D status or prostate cancer risk. The central hypothesis is that vitamin D deficiency will increase prostate cancer incidence and disease aggressiveness. We will definitively address this hypothesis by measuring all of the relevant mediators in a city with high rates of vitamin D deficiency in a case-control study of 40-79 year old African American and European American with incidence prostate cancer and age and ethnicity matched controls. We aim to 1. Evaluate the risk of aggressive prostate cancer and vitamin D levels in African American and European American men. 2. Assess single nucleotide polymorphism variation in candidate genes involved in vitamin D synthesis, metabolism and signaling and their mutual role along with vitamin D status in prostate cancer risk. At this point, we are able to report that 44% of Chicago area men are deficient in vitamin D and that skin color is the main determinant in African Americans and sun exposure is the main determinant in European Americans and supplementation can ameliorate this in both racial groups. We will have enough variance in vitamin D to evaluate our data fully for our specific aims.

15. SUBJECT TERMS
vitamin D deficiency, prostate cancer, health disparities, African American

16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	19	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

ANNUAL REPORT:

INTRODUCTION:

The purpose of the protocol funded by the training award was to determine the influence of vitamin D status and related genetic polymorphisms on overall risk of prostate cancer and risk of aggressive forms of prostate cancer. It involves three Chicago area academic affiliated urology clinics where 2025 men will be recruited. Thus far, we have recruited from all sites. Age 40-79 year old men are recruited prior to prostate biopsy and serum vitamin D and blood for genetic analysis is drawn. Also questionnaires on medical history/demographic information, sun exposure, and dietary calcium and vitamin D intake are ascertained. Finally, the melanin content of the skin is measured using a skin reflectance meter called a Dermaspectrometer, to measure baseline skin melanin content, which is known to inhibit vitamin D synthesis from sunlight. This physician research-training award would provide the recipient, Dr. Adam Murphy, with mentorship from Dr. Kittles from cancer genetics and from Dr. Catalona in clinical research in prostate cancer. This has resulted in several abstracts over the past year and one publication. As part of his training program, he will also be receiving some formal laboratory training from Dr. Kittles on several genetic data analysis techniques. This coming year will focus on laboratory techniques involved with genotyping. The training program also provided for several opportunities to deepen his connection with other research collaborators across institutions. I have been working on a community based participatory research project with Marcus Murray at Project Brotherhood, Inc focused on barriers to HIV and prostate cancer screening which is funded by our Northwestern University Specialized Program of Research Excellence in Prostate Cancer. I also have been awarded a new investigator award by the NIH Office of AIDS Research in collaboration with two Infectious Diseases physicians at Northwestern University. Moreover, it is providing for time for taking classes in the Masters of Science in Clinical Investigation program at Northwestern University to improve his skills in biostatistics, epidemiology and research methods.

Note: Please recall that there were multiple delays with the approval for the protocol since there was so many institutions involved and since the primary mentor left University of Chicago and went to University of Illinois at Chicago. Dr. Murphy initially tried to seek approval for all four participating institutions, which proved to be formidable. Dr. Murphy spent much of my time initially obtaining signatures from laboratory managers, biohazard and safety personnel to get the necessary forms signed for environmental compliance. There was also confusion as to whether the PI needed to submit the protocols for every participating site. Ultimately Dr. Melissa Baker decided that since the DOD was solely funding me to do the project and that their funds were not going to the other institutions. Thus, monitoring the other sites now falls under the Northwestern IRB purview. It was finally decided in July 2011 that since the protocol was identical at each site and since the principal investigator was responsible for most of the recruiting at each site that the other sites would not be under the purview of the Department of Defense. The only site that then required HRPO approval was Northwestern University, which occurred in Month 10.

BODY:

Year 2 accomplishments: (Months 13 - 24)

1. Recruitment: began recruitment under the DOD approved protocol and consent form at all participating sites.
2. Additional Training
    a. Worked in Dr. Kittles' laboratory to learn some of the lab techniques for DNA extraction, genotyping, and data analysis techniques for epidemiologic studies.
    b. Taking coursework at Northwestern University's Master's of Science in Clinical Investigation (Months 13 – 22)

i. Intermediate Biostatistics
ii. Intermediate Epidemiology
iii. Drug Development Process

3. Secondary Aim analysis of effects of socioeconomic status, insurance status, education level and race on aggressiveness of prostate cancer on biopsy and on prostatectomy surgical pathology has been postponed due to lack of significance of endpoints on preliminary analysis.
4. I performed a data analysis on vitamin D and prostate cancer risk for an abstract for the Intercultural Cancer Council Biennial Symposium on Minorities, the Medically Underserved & Health Equity.
   a. Specimen processing at ARUP laboratories in Salt Lake City, Utah
   b. Trained research assistant to gather data on initial pathology review and post prostatectomy pathology for Quality Control
   c. Genitourinary pathologists at participating sites evaluated pathology samples.
   d. Worked with Dr. Kittles and Dr. Catalona on selection of control patients, data analysis, and interpretation and podium presentation.
   e. PhD epidemiologist, Iman K. Martin PhD, assisted with statistical analysis for abstract.
5. IRB Renewal at Northwestern University (lead institution over participating sites).
   a. Continuing Review completed in Month 18

KEY RESEARCH ACCOMPLISHMENTS:

- I have completed the continuing review for Northwestern University and the participating sites for 2012 and have data on 356 patients from my preliminary data phase pre-approval (103 cases/176 controls/77 negative biopsies). Since HRPO approval I have recruited 93 cases/291 controls/93 negative biopsies. Of the 483 men recruited this past year 195 are African American men and 204 are European American men, and 84 others. 4 AA and 3 EA have pending biopsy results.

- I have submitted the following abstracts at national scientific meetings:
  - Murphy, A, Martin, I, Nyame, Y, Shah, E, Ruden, M, Newsome, J, Agate, S, Dixon, M, Hollowell, CMP, Catalona, W, Kittles, R. Vitamin D Deficiency and Prostate Cancer Risk in African American Men. Biennial Symposium on Minorities, The Medically Underserved and Health Equity Abstract, June 2012.

  - Nyame, Y, Kittles, R, **Murphy, A**. Evaluating Vitamin D Levels And Risk of Renal Cell Carcinoma Using An Electronic Data Warehouse. Biennial Symposium on Minorities, The Medically Underserved and Health Equity Abstract, June 2012.

  - Murphy, A, Nyame, Y, Smith, D, Castaneda, L, Kelley, B, Minaya, K, Hollowell, CMP, Kittles, R. Biological and Environmental Correlates of Vitamin D Status in African American and European American Men in Chicago. AACR Abstract, September 2011.

  - Batai, K, Beisner, E, Shah, E, Castaneda, L, Smith, D, **Murphy, A**, Kittles, R. IL-16 variants associated with prostate cancer risk in African Americans. AACR Abstract, September 2011.

- I have published a paper based on this data on predictors of vitamin D status:

- Murphy AB, Kelley B, Nyame YA, Martin IK, Smith DJ, Castaneda L, Zagaja GJ, Hollowell CM, Kittles RA. Predictors of Serum Vitamin D Levels in African American and European American Men in Chicago. Am J Mens Health. 2012 Mar 8. (See Appendix 1)

- I have hired a research assistant named Michael A. Dixon to aid in clerical, data management and recruiting efforts.

- I have also been involved in several articles with Dr. Kittles and Infectious Diseases colleagues at Northwestern University:
  - Taylor AK, Zembower TR, Nadler RB, Scheetz MH, Cashy JP, Bowen D, **Murphy AB**, Dielubanza E, Schaeffer AJ. Targeted antimicrobial prophylaxis using rectal swab (RS) cultures in men undergoing transrectal ultrasound guided prostate biopsy (TRUSP) significantly reduces the incidence of post procedure infectious complications and cost of care. J Urol. 2012 Apr;187(4):1275-9.
  - Murphy AB, Ukoli F, Freeman V, Bennett F, Aiken W, Tulloch T, Coard K, Angwafo F, Kittles RA. 8q24 risk alleles in West African and Caribbean men. Prostate. 2012 Jan 10. doi: 10.1002/pros.22486.
  - N'Diaye, A, Chen, GK, Palmer, CD, Ge, B, Tayo, B, Mathias, RA, Kittles, RA, **Murphy, A**, Nyante, S, Ogunniyi, A et al. Identification, replication, and fine-mapping of loci associated with adult height in individuals of African ancestry. Nature, April 2011.
  - Haiman, CA, Chen, GK, Blot, WJ, Strom, SS, Berndt, SI, Kittles, RA, Rybicki, BA, Isaacs, WB, Ingles, SA, Stanford, JL, Diver, WR, Witte, JS, Chanock, SJ, Kolb, S, Signorello, LB, Yamamura, Y, Neslund-Dudas, C, Thun, MJ, **Murphy, A**, Casey, G, Sheng, X, Wan, P, Pooler, LC, Monroe, KR, Waters, KM, Le Marchand, L, Kolonel, LN, Stram, DO, Henderson, BE. Characterizing genetic risk at known prostate cancer susceptibility loci in African Americans. PLoS Genet. 2011 May;7(5):e1001387.
  - Haiman, CA, Chen, GK, Blot, WJ, Strom, SS, Bernt, S, Kittles, RA, **Murphy, A**, Rybicki, BA, Isaacs, W, Ingles, SA, Stanford, JL, Diver, R, et al: Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. Nat Genet. 2011 Jun;43(6):570-3.

REPORTABLE OUTCOMES:

Published Article

Murphy AB, Kelley B, Nyame YA, Martin IK, Smith DJ, Castaneda L, Zagaja GJ, Hollowell CM, Kittles RA. Predictors of Serum Vitamin D Levels in African American and European American Men in Chicago. American Journal of Men's Health. 2012 Mar 8.

Abstract: Vitamin D deficiency is epidemiologically linked to prostate, breast, and colon cancer. When compared with European American (EA) men, African American (AA) men have increased risk of prostate cancer, but few studies evaluate vitamin D status in AA men. The authors evaluate the biological and environmental predictors of vitamin D deficiency in AA and EA men in Chicago, Illinois, a low ultraviolet radiation environment. Blood samples were collected from 492 men, aged between 40 and 79 years, from urology clinics at three hospitals in Chicago, along with demographic and medical information, body mass index, and skin melanin content using a portable narrow-band reflectometer. Vitamin D intake and ultraviolet radiation exposure were assessed using validated questionnaires. The results demonstrated that Black race, cold season of blood draw, elevated body mass index, and lack of vitamin D supplementation increase the risk of vitamin D deficiency. Supplementation is a high-impact, modifiable risk factor. Race and sunlight exposure should be taken into account for recommended daily allowances for vitamin D intake.

Abstracts

1. Murphy, A, Martin, I, Nyame, Y, Shah, E, Ruden, M, Newsome, J, Agate, S, Dixon, M, Hollowell, CMP, Catalona, W, Kittles, R. Vitamin D Deficiency and Prostate Cancer Risk in African American Men. Biennial Symposium on Minorities, The Medically Underserved and Health Equity Abstract, June 2012. (Appendix 2)

2. Murphy, A, Nyame, Y, Smith, D, Castaneda, L, Kelley, B, Minaya, K, Hollowell, CMP, Kittles, R. Biological and Environmental Correlates of Vitamin D Status in African American and European American Men in Chicago. AACR Abstract, September 2011. (Appendix 3)

CONCLUSIONS:

The HRPO approval to begin recruiting participants was just provided in month 11 of year 1. However, preliminary data collection was good and since approval, recruitment has been going pretty well. I have worked with my mentors on research training goals including learning DNA extraction, SNP selection, genetic data analysis, paper and abstract and podium presenting and review of the literature. I have also enrolled in multiple classes in the program in Master's of Science in Clinical Investigation at Northwestern University. We are set up to continue with the Department of Defense approved protocol.

In Chicagoland, 63% of African American men and 18% of European American men are deficient using the stringent Institute of Medicine definition, 25 hydroxyvitamin D < 20ng/ml in 40-79 y/o men presenting to the urology clinics. The African American men are vitamin D deficient at relatively high rates in the warm months in Chicago. The season was the biggest predictor of vitamin D level followed by use of vitamin D supplements in European Americans. The biggest predictor of vitamin D deficiency in African American men was skin color and they were more likely to be deficient using any of the potential cutoffs. This project will provide adequate numbers of men for detecting the effects of vitamin D status on prostate cancer risk.

Moreover, we recently presented preliminary data on the risk of vitamin D deficiency on prostate cancer risk in European American and African Americans. The overall findings show increased prostate cancer risk among European Americans when they were vitamin D deficient in the low UV months. The risk of prostate cancer risk was elevated for African Americans when they were deficient in the high UV months and there risk of aggressive disease went up when vitamin D deficient in the warm UV months. There was a trend for increased disease aggressiveness among European Americans in the low UV months too but the confidence intervals were too wide. This should improve with further participant accrual.

RELEVANT LITERATURE:

1. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J Clin Endocrinol Metab. 2010 Nov 29. [Epub ahead of print]

2. Berkovich L, Ben-Shabat S, Sintov AC. Induction of apoptosis and inhibition of prostate and breast cancer growth by BGP-15, a new calcipotriene-derived vitamin D3 analog. Anticancer Drugs. 2010 Jul;21(6):609-18.

3. Gavrilov V, Leibovich Y, Ariad S, Lavrenkov K, Shany S. A combined pretreatment of 1,25-dihydroxyvitamin D3 and sodium valproate enhances the damaging effect of ionizing radiation on prostate cancer cells.J Steroid Biochem Mol Biol. 2010 Jul;121(1-2):391-4. Epub 2010 Mar 7.

4. Hofmann JN, Yu K, Horst RL, Hayes RB, Purdue MP. Long-term variation in serum 25-hydroxyvitamin D concentration among participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer Epidemiol Biomarkers Prev. 2010 Apr;19(4):927-31. Epub 2010 Mar 23.

5. Muindi JR, Yu WD, Ma Y, Engler KL, Kong RX, Trump DL, Johnson CS. CYP24A1 inhibition enhances the antitumor activity of calcitriol. Endocrinology. 2010 Sep;151(9):4301-12. Epub 2010 Jun 30.

6. Luo W, Karpf AR, Deeb KK, Muindi JR, Morrison CD, Johnson CS, Trump DL. Epigenetic regulation of vitamin D 24-hydroxylase/CYP24A1 in human prostate cancer. Cancer Res. 2010 Jul 15;70(14):5953-62. Epub 2010 Jun 29.

7. Brock KE, Graubard BI, Fraser DR, Weinstein SJ, Stolzenberg-Solomon RZ, Lim U, Tangrea JA, Virtamo J, Ke L, Snyder K, Albanes D. Predictors of vitamin D biochemical status in a large sample of middle-aged male smokers in Finland. Eur J Clin Nutr. 2010 Mar;64(3):280-8. Epub 2010 Jan 6.

8. Kristal AR, Arnold KB, Neuhouser ML, Goodman P, Platz EA, Albanes D, Thompson IM. Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol. 2010 Sep 1;172(5):566-77. Epub 2010 Aug 6.

9. Soni MG, Thurmond TS, Miller ER 3rd, Spriggs T, Bendich A, Omaye ST. Safety of vitamins and minerals: controversies and perspective. Toxicol Sci. 2010 Dec;118(2):348-55. Epub 2010 Sep 22.

10. Chadha MK, Fakih M, Muindi J, Tian L, Mashtare T, Johnson CS, Trump D. Effect of 25-hydroxyvitamin D status on serological response to influenza vaccine in prostate cancer patients. Prostate. 2010 Sep 1. [Epub ahead of print]

11. Washington MN, Kim JS, Weigel NL. 1α,25-dihydroxyvitamin D3 inhibits C4-2 prostate cancer cell growth via a retinoblastoma protein (Rb)-independent G1 arrest. Prostate. 2011 Jan 1;71(1):98-110.

12. Risio M, Venesio T, Kolomoets E, Armaroli P, Gallo F, Balsamo A, Muto G, D'Urso L, Puppo P, Naselli A, Segnan N; BECaP Working Group. Genetic polymorphisms of CYP17A1, vitamin D receptor and androgen receptor in Italian heredo-familial and sporadic prostate cancers. Cancer Epidemiol. 2010 Nov 18. [Epub ahead of print]

13. Marcinowska-Suchowierska E, Walicka M, Tałałaj M, Horst-Sikorska W, Ignaszak-Szczepaniak M, Sewerynek E. Vitamin D supplementation in adults - guidelines. Endokrynol Pol. 2010 Nov-Dec;61(6):723-9.

14. Thorne JL, Maguire O, Doig CL, Battaglia S, Fehr L, Sucheston LE, Heinaniemi M, O'Neill LP, McCabe CJ, Turner BM, Carlberg C,Campbell MJ. Epigenetic control of a VDR-governed feed-forward loop that regulates p21(waf1/cip1) expression and function in non-malignant prostate cells. Nucleic Acids Res. 2010 Nov 17. [Epub ahead of print]

15. Gregory KJ, Zhao B, Bielenberg DR, Dridi S, Wu J, Jiang W, Huang B, Pirie-Shepherd S, Fannon M. Vitamin D binding protein-macrophage activating factor directly inhibits proliferation, migration, and uPAR expression of prostate cancer cells. PLoS One. 2010 Oct 18;5(10):e13428.

16. Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T, Trikalinos TA. Vitamin D and calcium: a systematic review of health outcomes. Evid Rep Technol Assess (Full Rep). 2009 Aug;(183):1-420.

17. Flores O, Burnstein KL. GADD45gamma: a new vitamin D-regulated gene that is antiproliferative in prostate cancer cells. Endocrinology. 2010 Oct;151(10):4654-64. Epub 2010 Aug 25.

18. Kimura M, Rabbani Z, Mouraviev V, Tsivian M, Caso J, Satoh T, Baba S, Vujaskovic Z, Baust JM, Baust JG, Polascik TJ. Role of vitamin D(3) as a sensitizer to cryoablation in a murine prostate cancer model: preliminary in vivo study. Urology. 2010 Sep;76(3):764.e14-20.

19. Brock KE, Graubard BI, Fraser DR, Weinstein SJ, Stolzenberg-Solomon RZ, Lim U, Tangrea JA, Virtamo J, Ke L, Snyder K,Albanes D. Predictors of vitamin D biochemical status in a large sample of middle-aged male smokers in Finland. Eur J Clin Nutr. 2010 Mar;64(3):280-8. Epub 2010 Jan 6.

20. Luo W, Karpf AR, Deeb KK, Muindi JR, Morrison CD, Johnson CS, Trump DL. Epigenetic regulation of vitamin D 24-hydroxylase/CYP24A1 in human prostate cancer. Cancer Res. 2010 Jul 15;70(14):5953-62. Epub 2010 Jun 29.

21. Murphy AB, Ukoli F, Freeman V, Bennett F, Aiken W, Tulloch T, Coard K, Angwafo F, Kittles RA. 8q24 risk alleles in West African and Caribbean men. Prostate. 2012 Jan 10.

22. Haiman, CA, Chen, GK, Blot, WJ, Strom, SS, Bernt, S, Kittles, RA, Murphy, A, Rybicki, BA, Isaacs, W, Ingles, SA, Stanford, JL, Diver, R, et al: Genome-wide association study of prostate cancer in men of African ancestry identifies a susceptibility locus at 17q21. Nat Genet. 2011 Jun;43(6):570-3. 3. Haiman, CA, Chen, GK, Blot, WJ, Strom, SS, Berndt, SI, Kittles, RA, Rybicki, BA, Isaacs, WB, Ingles, SA, Stanford, JL, Diver, WR, Witte, JS, Chanock, SJ, Kolb, S, Signorello, LB, Yamamura, Y, Neslund-Dudas, C, Thun, MJ, Murphy, A, Stram, DO, Henderson, BE. Characterizing genetic risk at known prostate cancer susceptibility loci in African Americans. PLoS Genet. 2011 May;7(5):e1001387.

23. Murphy, A, Kelley B, Nyame YA, Martin IK, Smith DJ, Castaneda L, Zagaja GJ, Hollowell CM, Kittles RA. Predictors of Serum Vitamin D in African American and European American Men in Chicago. Am J Mens Health. 2012 Mar 8.

24. Gandini S, Boniol S, Haukka J, Cox B, Sneyd MJ, Mullie P, Autier P. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int. J. Cancer. 2011 Mar 15;128(6):1414-24. doi: 10.1002/ijc.25439.

Predictors of Serum Vitamin D Levels in African American and European American Men in Chicago

Adam B. Murphy, Brian Kelley, Yaw A. Nyame, Iman K. Martin, Demetria J. Smith, Lauren Castaneda, Gregory J. Zagaja, Courtney M. P. Hollowell and Rick A. Kittles

Am J Mens Health 2012 6: 420 originally published online 7 March 2012
DOI: 10.1177/1557988312437240

Predictors of Serum Vitamin D Levels in African American and European American Men in Chicago

American Journal of Men's Health
6(5) 420–426

DOI: 10.1177/1557988312437240
http://ajmh.sagepub.com
SAGE

Adam B. Murphy, MD, MBA[1], Brian Kelley, MA[1], Yaw A. Nyame, MHSA[1], Iman K. Martin, MPH, MSc[2], Demetria J. Smith, MA[2], Lauren Castaneda, MA[2], Gregory J. Zagaja, MD[3], Courtney M. P. Hollowell, MD[4], and Rick A. Kittles, PhD[2]

Abstract

Vitamin D deficiency is epidemiologically linked to prostate, breast, and colon cancer. When compared with European American (EA) men, African American (AA) men have increased risk of prostate cancer, but few studies evaluate vitamin D status in AA men. The authors evaluate the biological and environmental predictors of vitamin D deficiency in AA and EA men in Chicago, Illinois, a low ultraviolet radiation environment. Blood samples were collected from 492 men, aged between 40 and 79 years, from urology clinics at three hospitals in Chicago, along with demographic and medical information, body mass index, and skin melanin content using a portable narrow-band reflectometer. Vitamin D intake and ultraviolet radiation exposure were assessed using validated questionnaires. The results demonstrated that Black race, cold season of blood draw, elevated body mass index, and lack of vitamin D supplementation increase the risk of vitamin D deficiency. Supplementation is a high-impact, modifiable risk factor. Race and sunlight exposure should be taken into account for recommended daily allowances for vitamin D intake.

Keywords

health inequality/disparity, health care issues, health promotion and disease prevention, nutrition, preventive medicine, public health

Introduction

Vitamin D regulates parathyroid hormone levels and is known to have a role in bone formation, resorption, and mineralization. Vitamin D deficiency results in decreased bone density, and it is the primary cause of rickets in children and osteomalacia and osteoporosis in adults (Heaney, 2004). In recent years, scientists have been investigating the role of vitamin D in disease prevention. Vitamin D deficiency has been implicated in diabetes, hypertension, end-stage renal disease, tuberculosis, and peripheral artery disease (Holick, 2006; Holick & Chen, 2008; Melamed et al., 2009; Reis, Michos, von Muhlen, & Miller, 2008). Studies have also found increased incidence of breast, colon, and prostate cancer among people living at higher latitudes in the United States (Holick, 2006; Schwartz & Hulka, 1990). Miller et al. (1992) found that prostate cells have the vitamin D receptor (VDR), and the VDR has been found in a number of other nonrenal tissues. Other studies suggest that $1,25(OH)_2$-D, the most active metabolite of vitamin D, appears to promote cell differentiation and inhibit proliferation (Holick, 2006). Multiple studies have assessed determinants of low 25-hydroxyvitamin D (25-OH D) levels (Benjamin et al., 2009; Bischoff-Ferrari, Dietrich, Orav, & Dawson-Hughes, 2004; Chapuy et al., 1997; Dawson-Hughes, 2004; Dawson-Hughes et al., 2005; Hannan et al., 2008; Harris, Soteriades, Coolidge, Mudgal, & Dawson-Hughes, 2000; Holick, 2006; Holick et al., 2005; Kumari, Judd, & Tangpricha, 2008; Malabanan, Veronikis, & Holick, 1998; Nesby-O'Dell et al., 2002; Saadi et al., 2006; Vieth, Ladak, & Walfish, 2003; Zadshir,

[1]Northwestern University, Chicago, IL, USA
[2]University of Illinois at Chicago, Chicago, IL, USA
[3]University of Chicago Hospitals, Chicago, IL, USA
[4]Cook County Health and Hospitals System, Chicago, IL, USA

Corresponding Author:
Adam B. Murphy, Department of Urology, Feinberg School of Medicine, Northwestern University, 303 E. Chicago Avenue, 16-710, Chicago, IL 60611, USA
Email: a-murphy2@md.northwestern.edu

Tareen, Pan, Norris, & Martins, 2005). These studies have been carried out mainly in Caucasian women and have demonstrated that age, sex, ethnicity, latitude, season, body mass index (BMI), and dietary and supplemental vitamin D intake were important factors influencing vitamin D status. There are a few studies evaluating the prevalence of vitamin D insufficiency in men (Benjamin et al., 2009; Holick & Chen, 2008; Miller et al., 1992; National Institutes of Health, 2010; Reis et al., 2008; Schwartz & Hulka, 1990) and far fewer in African American (AA) men (Benjamin et al., 2009).

There are a number of factors that affect circulating levels of serum vitamin D. In addition to genetic variation in the vitamin D pathway, three primary modifiers of serum vitamin D levels are diet, exposure to UV radiation (UVR), and skin color. The National Institutes of Health (NIH) lists fish liver oils and fatty fish, such as salmon, tuna, and mackerel, as the best sources of dietary vitamin D. Vitamin D can also be found in eggs, irradiated mushrooms, yeast, and to lesser amounts in fortified cow's milk (NIH, 2010). On November 30, 2010, the Institute of Medicine (2011) released their updated Dietary Reference Intake, which recommends that individuals younger than 70 years of age obtain 600 IU of vitamin D from their diet. This represents a 200 IU increase in previous recommended daily allowance for vitamin D_3. This is only expected to increase serum 25-hydroxyvitamin D (25-OH D) levels by 1.4 ng/mL on average. Also, because of a relative paucity of Level 1 evidence for defining vitamin D deficiency, the Institute of Medicine has lowered the deficiency cutoff for serum 25-OH D levels from > 30 ng/mL to >20 ng/mL. Obesity is associated with vitamin D deficiency. Only 28% of obese adolescents reached sufficient vitamin D serum levels when given daily supplementation of vitamin D (800 IU; Harel, Flanagan, Forcier, & Harel, 2011). In a large Swedish prostate cancer study, it was shown that men living at high latitude have high prevalence of vitamin D deficiency. Taken together, with data on Swedish prostate cancer and with studies done on women from the United Arab Emirates, the data suggest that these recommendations might need to be altered based on BMI, sun exposure, and skin color (Saadi et al., 2006).

Exposure to UVR accounts for approximately 90% of circulating levels of 25-OH D (Holick, 2003). This exposure is affected by the time that one spends outside, the amount of clothing one wears, and the use of sunscreen. Individuals who live farther from the equator receive less UV exposure on average than those who reside closer to it. Altitude, local weather trends, and latitude also affect UVR exposure. Living north of about 37° latitude limits UV-B radiation exposure from around November through February because the sun's zenith angle is so low that the atmosphere absorbs most UV-B rays before it reaches the Earth's surface. Darker skin pigmentation resulting from increased melanin production in the skin melanocytes can reduce the efficacy of UV-B radiation–induced vitamin D_3 synthesis. Skin with high melanin content can reduce vitamin D_3 synthesis by up to 99%, much in the way that SPF-15 (sun protection factor-15) sunscreen does (Holick, 2006).

Although vitamin D deficiency affects a significant portion of various populations worldwide, AAs have been identified as a group with a particularly high risk of vitamin D deficiency (Holick, 2006). A study done in young women in Boston found the serum 25-OH D levels of Black women to be less than half that of their White counterparts regardless of season (Harris et al., 2000). Additionally, many of the diseases thought to be associated with vitamin D deficiency are more prevalent among AAs (Melamed et al., 2009). These observations highlight the importance of investigating the epidemiology of vitamin D deficiency in AAs; however, there are surprisingly few studies involving this population, especially AA men. Previous studies have not had a sufficient number of AAs to allow ancestry-specific statistical analysis, or they have not thoroughly investigated the effect of nongenetic factors (Harris et al., 2000; John, Schwartz, Koo, Van Den Berg, & Ingles, 2005). In this study, we explore the three potential environmental modifiers of serum vitamin D levels in AA men to help answer this question.

Study Population

This is a cross-sectional study evaluating modifiers of serum vitamin D within a larger cross-sectional study evaluating the biological and environmental mediators of serum vitamin D and prostate cancer risk. The study population consists of 40- to 79-year-old, ambulatory, unrelated men in Chicago, Illinois. Recruitment took place at Northwestern Memorial Hospital, Cook County Health and Hospitals System, and University of Chicago Hospital, in Chicago, Illinois, through the respective outpatient urology clinics. A subset of the control subjects was recruited through prostate cancer screening events. All patients recruited were males that self-identified as AA, European American (EA), or Hispanic and consented to the venipuncture and the institutional review board (IRB)–approved study. We excluded the 66 Hispanic men from this analysis to await further accrual. Exclusion criteria were patients with hyperparathyroidism, liver failure, chronic kidney disease, history of rickets, cancers except nonmelanoma skin cancer, and history of inborn error of calcium or vitamin D metabolism. Five hundred and fifty-eight patients (282 AA, 210 EAs, and 66 Hispanic men) were recruited in total. The study was approved by each of the institution's IRB, and all participants provided written informed consent.

Methods

Research coordinators conducted in-person interviews at the time of recruitment and administered structured questionnaires that ascertained calcium and vitamin D supplementation intake, ancestry, family history of cancer, medical history, occupation, income, education, alcohol consumption and tobacco use, marital status, and lifetime history of sun exposure. Because of previous data implicating increased body fat content as a contributing factor to vitamin D deficiency (Holick, 2006), standing height and weight were measured for BMI calculations. UVR exposure was assessed using a validated questionnaire that recorded reported cumulative sun exposure over various age ranges. Skin color was also measured, as it has been shown that increased skin pigmentation reduces the cutaneous synthesis of vitamin D (Clemens, Adams, Henderson, & Holick, 1982). Skin pigmentation was measured using a portable narrow-band reflectometer called the Dermaspectrometer (Cyberderm, Broomall, PA). The Dermaspectrometer measures skin color through skin reflectance, where output is expressed in terms of erythema (E) and melanin (M) indices from 0% to 100%, where higher values denote higher pigment content (Takiwaki, 1998). Three measurements of skin pigmentation were taken at the inner upper arm and three at the center of the forehead to establish constitutive and facultative pigmentation, respectively. The difference between facultative and constitutive M indices was used to calculate an M index, which represents the additional melanin produced in sun-exposed skin, and it would be positively correlated with the cumulative sun exposure a person has experienced over his or her lifetime. This melanin content–derived index is an objective, quantitative index to measure cumulative lifetime UVR exposure. The reported and the melanin content–derived UVR exposure indices were used in all analyses.

A Block calcium and vitamin D screener adapted from *National Health and Nutrition Examination Survey* 1999-2001 dietary recall data and validated for use in the AA population assessed usual 25-OH D intake during the reference year, defined as the year prior to recruitment into the study (Block et al., 1986; Block, Hartman, & Naughton, 1990; Coates et al., 1991). The screener consisted of 19 food items, 3 supplements questions, and questions to adjust for food fortification practices.

A peripheral blood sample was collected at the time of recruitment for serum 25-OH D measurement. Serum samples were stored in small test tubes at −20°C until 25-OH D measurement. Total 25-OH D was assessed by chemiluminescent immunoassay by the Associated Regional and University Pathologists laboratory in conjunction with the University of Utah. The season of blood draw was evaluated in two seasons as cold (1 November through 30 April) and warm (1 May through 31 October) based on UVR data from Chicago.

Results

In our cohort of EA and AA men with vitamin D data, 81.4% of all men meet the laboratory definition of vitamin D deficiency with levels <30 ng/mL (see Table 1). Ninety-three percent of AA men and 66% of EA would be considered deficient. Using the Institute of Medicine definition of deficiency being <20 ng/mL, 18% of the EA men were deficient versus 63% of AA men. The mean and median serum 25-OH D level was 21 ng/mL. The median level for AA men was 17.2 ng/mL, whereas for EA men it was 24.2 ng/mL ($p < .001$). There was a seasonal pattern witnessed in serum 25-OH D levels (see Figure 1). The mean and median for dietary vitamin D intake was 248 IU/day and 174 IU/day, respectively. The mean total vitamin D intake (dietary and supplements) was 410 IU/day, with a median of 166 IU/day. For AA men, the mean total vitamin D intake was 240 IU/day, with a median of 74 IU/day. EA men had a mean total vitamin D intake of 572 IU/day (median of 225 IU/day). The differences between EA and AA men in supplemental intakes were statistically significant (Table 1).

Pearson correlations for the total group reveal that higher vitamin D levels were significantly negatively correlated with BMI and positively associated with income, the use of vitamin D supplementation, and total lifetime sun exposure as measured by melanin content differences in sun-exposed and nonexposed skin (all $p < .01$). The distributions of vitamin D level, dietary and supplemental vitamin D intake, and income were relatively distinct between EA and AA men. Because of this, we stratified the pairwise correlations by race with separate analyses for AA and EA men (see Table 2). In AA men, none of the covariates reached statistical significance for their correlation with 25-OH D levels. Among EA men, only income was positively correlated with vitamin D levels ($p = .04$).

On univariate linear regression (Table 3), 25-OH D levels were most strongly predicted by AA race ($\beta = -6.95$, $p < .0005$). The linear model was constructed with gradual addition of the covariates. The relationship between AA race ($\beta = -4.85$, $p = .02$) and 25-OH D level was weakened by addition of season of blood draw and sunscreen use. With the addition of total vitamin D supplement intake to the model, AA race retains borderline significance ($\beta = -3.68$, $p = .066$). With the addition of baseline skin melanin content and reported lifetime sun exposure (both $p < .05$), AA race loses its significance ($p = .74$).

When stratified by race, the linear regression ($R^2 = 0.30$) for EA reveals that 25-OH D levels are most strongly predicted by season of blood draw ($\beta = 6.74$, $p < .0005$). This was followed in strength by the M index–derived lifetime

Table 1. Characteristic Comparison Between African American and European American Men

Characteristic	African American Men (n = 282)	European American Men (n = 210)	p Value
Age (years)	59.0 ± 11.1	60.8 ± 8.8	.958
BMI (kg/m^2)	28.6 ± 5.6	27.8 ± 5.4	.041*
Serum 25-OH vitamin D level (ng/mL)	17.2 ± 8.1	24.2 ± 10.1	<.001*
Dietary vitamin D intake (IU/day)	93.3 ± 89.8	100.4 ± 101.8	.115
Supplemental vitamin D intake	168.5 ± 582.5	475.2 ± 2965.8	<.001*
Multivitamin use, n (%) (contains 400 IU vitamin D_2)	92 (43)	110 (53)	.036*
Vitamin D supplement use, n (%)	98 (35)	115 (55)	.019*
Calcium supplement use, n (%)	105 (49)	122 (59)	.036*
Sunscreen use, n (%)	37 (13)	142 (68)	<.001*
High sun exposure, n (%) (reported UV-exposure index ≥ 10)	56 (20)	21 (10)	.023*

Note. BMI = body mass index; IU = international unit; UV = ultraviolet radiation; 25-OH vitamin D = 25-hydroxyvitamin D.
*p < .05.

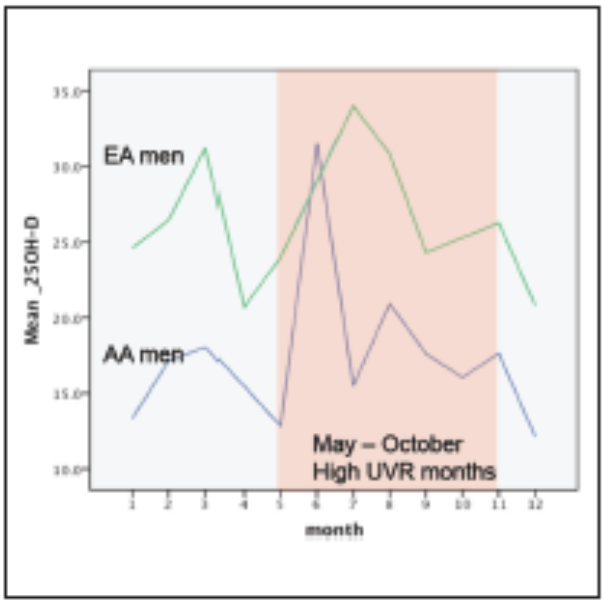

Figure 1. European American and African American vitamin D levels by month

sun exposure (β = 5.8, p = .02), income (β = 1.13, p = .002), and BMI (β = –0.47, p = .009). The linear regression for AA men reveals that 25-OH D levels (R^2 = 0.43) were associated with previous residence in the tropics (β = 5.60, p = .04), dietary vitamin D intake (β = 0.02, p = .03), and supplemental vitamin D intake (β = 0.05, p = .01).

On binomial logistic regression for vitamin D deficiency (25-OH D < 20 ng/mL), we constructed the regression model with season as the predictor and also stratified the analysis by race. In EA men, vitamin D deficiency was predicted by cold season of blood draw (odds ratio [OR] = 3.34, p = .02) and by the lack of vitamin D supplement use (OR = 2.38, p = .035). In AA men, vitamin D deficiency was predicted by the lack of vitamin D supplement use only (OR = 5501.0 p = .05).

Discussion

Forty-four percent of our population was vitamin D deficient using the recently defined Institute of Medicine deficiency cutoff (25-OH D < 20 ng/mL). Using the laboratory standard definition (<30 ng/mL), more than 90% of the AA men have deficiency. The median total vitamin D intake was 166 IU/day in our population. The median 25-OH D level was 21 ng/mL, which is well below the usual 30 ng/mL vitamin D sufficiency level. If we assume that the men consumed an additional 434 IU to get everyone in our population to the 600 IU recommended daily allowance, we would expect an increase of 3.04 ng/mL in serum 25-OH D levels (0.7 ng/mL per 100 IU of calciferol consumed). This would leave 37.1% of men deficient using <20 ng/mL as the deficiency cutoff. This is not an appropriate recommendation for this population of men.

Vitamin D level is predicted by season, AA race, income, BMI, and vitamin D supplemental intake. Because the distributions of vitamin D levels were different between EA and AA men, we ran regressions stratifying by race. When stratifying by season and controlling for age, we find that EA and AA men have a different constellation of variables associated with their vitamin D status. For EA men, lifetime sun exposure (M index) and income reach statistical significance with small beta coefficients (β< 1, p < .02, for both) with the largest effect for season of blood draw (β = 3.40, p = .047). When stratified by season, vitamin D supplement use (β = 6.34, p = .02)

Table 2. Pearson Correlations With Serum 25-OH Vitamin D and Other Covariates in African American Men (*Unshaded Area*) and European American Men (*Shaded Area*)

	Age	25-OH D	Dietary Vitamin D Intake	Supplemental Vitamin D Intake	BMI	M Index	Reported UV Exposure	Comorbidity Index	Pack Years of Smoking	Income
Age	1.00	.13	−.03	.11	−.05	.09	.05	.37*	.27*	−.02
25-OH D	.01	1.00	.07	.14	−.08	.11	.06	−.01	−.11	.28*
Dietary vitamin D intake	−.17	.13	1.00	.03	−.08	.05	−.06	.08	−.06	.02
Supplemental vitamin D intake	−.05	.23	.04	1.00	.07	.003	−.001	−.08	−.13	.01
BMI	−.13	.01	−.06	.28*	1.00	.05	−.01	.19*	.02	−.05
M Index	.16*	−.03	−.09	.05	.07	1.00	−.03	.13 ($p < .06$)	−.10	.09
Reported UV exposure	.02	.03	.06	.05	.10	−.06	1.00	−.05	.11	−.05
Comorbidity Index	.39*	−.04	.01	.08	.20*	.07	−.03	1.00	.21*	−.08
Pack-years of smoking	−.07	−.05	−.07	−.02	−.06	.10	−.04	−.05	1.00	−.19*
Income	−.08	.16	−.05	−.05	−.19*	−.23*	.01	−.13*	−.03	1.00

Note. BMI = body mass index; 25-OH D = serum 25 hydroxyvitamin D level; M Index = melanin content in sun-exposed skin – melanin content in nonexposed skin (correlated with total lifetime sun exposure).
*$p < .05$.

Table 3. Linear Regression Model With Serum 25-OH D Concentration as Outcome ($R^2 = 0.367$)

	β Estimate	Standard Error	*p* Value
Total vitamin D intake (IU/day), dietary and supplemental	0.002	0.003	.001*
Age (years)	0.050	0.057	.379
Vitamin D supplement use (0 = no, 1 = yes)	2.89	1.89	.129
AA race (0 = EA, 1 = AA)	−4.46	1.27	<.001*
BMI (kg/m^2)	−0.201	0.092	.029*
Reported UV exposure	0.281	0.184	.128
Use of sunscreen	0.867	1.19	.47
High UVR months	4.33	1.02	<.001*

Note. BMI = body mass index; IU = International Unit; AA = African American; EA = European American; UVR = ultraviolet radiation. In AA men only total vitamin D intake and high UVR months were significant in the model (both $p \leq .02$). In EA men only income and reported UV exposure were significant (both $p < .01$).
*$p < .05$.

reaches statistical significance during the cold months in EA men. In AA men, total vitamin D intake and sunscreen use are statistically significant but with small beta coefficients ($\beta < 0.03$, $p < .03$, for both) with the largest effect for season of blood draw ($\beta = 3.40$, $p < .047$). This is likely due to the low amount of dietary and supplement use among AA men.

In our analysis of vitamin D deficiency (25-OH D level < 30 ng/mL), we found that season of blood draw and lack of vitamin D supplement use was significant for EA men; lack of vitamin D supplement use predicted deficiency among AAs. The season of blood draw did not reach statistical significance in AA men ($p = .18$) but has an OR of 32.8 for deficiency during the cold months relative to the warm months. Since season is not an easily modifiable risk factor, supplementation may be the easiest way to overcome this issue. In addition to its well-established negative effects on the musculoskeletal system, vitamin D deficiency is associated with an increased risk of colorectal and breast cancer, autoimmune diseases, and cardiovascular disease (Lowe et al., 2005; Zittermann, 2003). AA people are at increased risk

for many of these diseases. It is essential, therefore, to maintain normal vitamin D status.

Measures to prevent vitamin D deficiency include increased skin exposure to sunlight, increased fortification of food items with vitamin D, and vitamin D supplementation. In the absence of adequate exposure to sunlight, there is mounting evidence that at least 1,000 IU of dietary or supplemental vitamin D intake is required daily to prevent vitamin D deficiency (Glerup et al., 2000; Holick, 2002; Hollis, 2005; Vieth, 1999). Given the serum levels of 25-OH D in our population and an estimated 0.7 ng/mL increase in serum 25-OH D level per 100 IU of vitamin D_3, we estimate 2,000 IU per day to reach minimum sufficiency (≥20 ng/mL) standards in nearly 95% of the Chicago population. Vitamin D supplementation currently remains the most appropriate mode for preventing vitamin D deficiency in high-risk groups such as AAs and individuals living in UV-poor environments. The optimal dosing regimen, including single or intermittent high-dose supplementation of vitamin D, needs to be defined in these groups. Race and residence in UV-poor environments should be taken into account when suggesting daily allowances of vitamin D.

Limitations

A limitation of our study may be the fact that dietary intake accuracy is threatened by recall bias. We use the validated semiquantitative Block Food Frequency Questionnaire for assessing vitamin D and calcium intake. Another limitation is that our determination of serum 25-OH D relied on a single measurement, which may not adequately reflect long-term exposure.

Conclusion

Vitamin D deficiency is present in 44% of Chicago-area men across all ethnicities using the strictest definition (serum 25-OH D < 20 ng/mL). Among AA men, 63% are vitamin D deficient using the 20 ng/mL cutoff and 93% of AA men are deficient using normal deficiency standards (<30 ng/mL), which is a significant cause for concern. Sunlight exposure through season or reported UV exposure in EA and vitamin D supplementation in both racial groups are statistically significantly associated with lower risk of vitamin D deficiency and higher overall 25-OH D levels and represent modifiable risk factors. Vitamin D supplementation counteracts the risk of vitamin D deficiency among AA men. Race and sunlight exposure should be taken into account for recommended daily allowances for vitamin D intake.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article:

This study was funded by the U.S. Department of Defense (Grant W81XWH-10-1-0532) and Northwestern University SPORE NIH grant (P50CA090386).

References

Benjamin, A., Moriakova, A., Akhter, N., Rao, D., Xie, H., Kukreja, S., & Barengolts, E. (2009). Determinants of 25-hydroxyvitamin D levels in African-American and Caucasian male veterans. *Osteoporosis International, 20,* 1795-1803.

Bischoff-Ferrari, H. A., Dietrich, T., Orav, E. J., & Dawson-Hughes, B. (2004). Positive association between 25-hydroxy vitamin D levels and bone mineral density: A population-based study of younger and older adults. *American Journal of Medicine, 116,* 634-639.

Block, G., Hartman, A. M., Dresser, C. M., Carroll, M. D., Gannon, J., & Gardner, L. (1986). A data-based approach to diet questionnaire design and testing. *American Journal of Epidemiology, 124,* 453-469.

Block, G., Hartman, A. M., & Naughton, D. (1990). A reduced dietary questionnaire: Development and validation. *Epidemiology, 1,* 58-64.

Chapuy, M. C., Preziosi, P., Maamer, M., Arnaud, S., Galan, P., Hercberg, S., & Meunier, P. J. (1997). Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporosis International, 7,* 439-443.

Clemens, T. L., Adams, J. S., Henderson, S. L., & Holick, M. F. (1982). Increased skin pigment reduces the capacity of skin to synthesise vitamin D_3. *Lancet, 1,* 74-76.

Coates, R. J., Eley, J. W., Block, G., Gunter, E. W., Sowell, A. L., Grossman, C., & Greenberg, R. S. (1991). An evaluation of a food frequency questionnaire for assessing dietary intake of specific carotenoids and vitamin E among low-income black women. *American Journal of Epidemiology, 134,* 658-671.

Dawson-Hughes, B. (2004). Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. *American Journal of Clinical Nutrition, 80*(6 Suppl.), 1763S-1766S.

Dawson-Hughes, B., Heaney, R. P., Holick, M. F., Lips, P., Meunier, P. J., & Vieth, R. (2005). Estimates of optimal vitamin D status. *Osteoporosis International, 16,* 713-716.

Glerup, H., Mikkelsen, K., Poulsen, L., Hass, E., Overbeck, S., Andersen, H., . . . Eriksen, E. F. (2000). Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. *Calcified Tissue International, 66,* 419-424.

Hannan, M. T., Litman, H. J., Araujo, A. B., McLennan, C. E., McLean, R. R., McKinlay, J. B., . . . Holick, M. F. (2008). Serum 25-hydroxyvitamin D and bone mineral density in a racially and ethnically diverse group of men. *Journal of Clinical Endocrinology and Metabolism, 93,* 40-46.

Harel, Z., Flanagan, P., Forcier, M., & Harel, D. (2011). Low vitamin D status among obese adolescents: Prevalence and response to treatment. *Journal of Adolescent Health, 48,* 448-452.

Harris, S. S., Soteriades, E., Coolidge, J. A., Mudgal, S., & Dawson-Hughes, B. (2000). Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. *Journal of Clinical Endocrinology and Metabolism, 85,* 4125-4130.

Heaney, R. P. (2004). Functional indices of vitamin D status and ramifications of vitamin D deficiency. *American Journal of Clinical Nutrition, 80*(6 Suppl.), 1706S-1709S.

Holick, M. F. (2002). Vitamin D: The underappreciated D-lightful hormone that is important for skeletal and cellular health. *Current Opinion in Endocrinology & Diabetes, 9,* 87-98.

Holick, M. F. (2003). Vitamin D: A millennium perspective. *Journal of Cellular Biochemistry, 88,* 296-307.

Holick, M. F. (2006). High prevalence of vitamin D inadequacy and implications for health. *Mayo Clinic Proceedings, 81,* 353-373.

Holick, M. F., & Chen, T. C. (2008). Vitamin D deficiency: A worldwide problem with health consequences. *American Journal of Clinical Nutrition, 87,* 1080S-1086S.

Holick, M. F., Siris, E. S., Binkley, N., Beard, M. K., Khan, A., Katzer, J. T., . . . de Papp, A. E. (2005). Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *Journal of Clinical Endocrinology and Metabolism, 90,* 3215-3224.

Hollis, B. W. (2005). Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: Implications for establishing a new effective dietary intake recommendation for vitamin D. *Journal of Nutrition, 135,* 317-322.

Institute of Medicine. (2011). *DRIs for calcium and vitamin D.* Retrieved from http://iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/DRI-Values.aspx

John, E. M., Schwartz, G. G., Koo, J., Van Den Berg, D., & Ingles, S. A. (2005). Sun exposure, vitamin D receptor gene polymorphisms, and risk of advanced prostate cancer. *Cancer Research, 65,* 5470-5479.

Kumari, M., Judd, S. E., & Tangpricha, V. (2008). Vitamin D status in United States war veterans. *Endocrine Practice, 14,* 127-128.

Lowe, L. C., Guy, M., Mansi, J. L., Peckitt, C., Bliss, J., Wilson, R. G., & Colston, K. W. (2005). Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. *European Journal of Cancer, 41,* 1164-1169.

Malabanan, A., Veronikis, I. E., & Holick, M. F. (1998). Redefining vitamin D insufficiency. *Lancet, 351,* 805-806.

Melamed, M. L., Astor, B., Michos, E. D., Hostetter, T. H., Powe, N. R., & Muntner, P. (2009). 25-Hydroxyvitamin D levels, race, and the progression of kidney disease. *Journal of the American Society of Nephrology, 20,* 2631-2639.

Miller, G. J., Stapleton, G. E., Ferrara, J. A., Lucia, M. S., Pfister, S., Hedlund, T. E., & Upadhya, P. (1992). The human prostatic carcinoma cell line LNCaP expresses biologically active, specific receptors for 1-alpha,25-dihydroxyvitamin D_3. *Cancer Research, 52,* 515-520.

National Institutes of Health. (2010). *Dietary supplement fact sheet: Vitamin D.* Retrieved from http://ods.od.nih.gov/factsheets/vitamind/

Nesby-O'Dell, S., Scanlon, K. S., Cogswell, M. E., Gillespie, C., Hollis, B. W., Looker, A. C., . . . Bowman, B. A. (2002). Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988-1994. *American Journal of Clinical Nutrition, 76,* 187-192.

Reis, J. P., Michos, E. D., von Mühlen, D., & Miller, E. R., III. (2008). Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease. *American Journal of Clinical Nutrition, 88,* 1469-1477.

Saadi, H. F., Nagelkerke, N., Benedict, S., Qazaq, H. S., Zilahi, E., Mohamadiyeh, M. K., & Al-Suhaili, A. I. (2006). Predictors and relationships of serum 25 hydroxyvitamin D concentration with bone turnover markers, bone mineral density, and vitamin D receptor genotype in Emirati women. *Bone, 39,* 1136-1143.

Schwartz, G. G., & Hulka, B. S. (1990). Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Research, 10,* 1307-1311.

Takiwaki, H. (1998). Measurement of skin color: Practical application and theoretical considerations. *Journal of Medical Investigation, 44,* 121-126.

Vieth, R. (1999). Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *American Journal of Clinical Nutrition, 69,* 842-856.

Vieth, R., Ladak, Y., & Walfish, P. G. (2003). Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *Journal of Clinical Endocrinology and Metabolism, 88,* 185-191.

Zadshir, A., Tareen, N., Pan, D., Norris, K., & Martins, D. (2005). The prevalence of hypovitaminosis D among US adults: Data from the NHANES III. *Ethnicity & Disease, 15*(4 Suppl. 5), 97-101.

Zittermann, A. (2003). Vitamin D in preventive medicine: Are we ignoring the evidence? *British Journal of Nutrition, 89,* 552-572.

Appendix 2: ICC Abstract

Vitamin D Deficiency and Prostate Cancer Risk in African American Men

Adam B. Murphy MD, MBA[1], Iman K. Martin MPH, PhD[2], Yaw Nyame MHSA[1], Ebony Shah MS[2], Maria Ruden MS[2], Jennifer Newsome MS[2], Sara Agate BA[1], Michael Dixon BA[1], Courtney MP Hollowell MD[3], William J. Catalona MD[1], Rick A. Kittles PhD[2].

[1]Department of Urology, Northwestern Feinberg School of Medicine, Chicago, IL; [2]Department of Medicine, Section of Hematology & Oncology, University of Illinois at Chicago, Chicago, IL; [3]Division of Urology, Cook County Health and Hospitals System, Chicago, IL.

Introduction: Vitamin D deficiency is inconclusively linked to prostate cancer (PCa) because most studies lack relevant covariates and men at high risk for vitamin D deficiency and PCa. Thus, we investigated vitamin D and PCa risk in AA men in Chicago, IL.

Methods: From 2009-2012, we conducted a cross-sectional study of 278, 40-79y/o AA men (190 healthy controls & 88 incident PCa cases) in 3 Urology clinics. Serum 25-hydroxyvitamin D (25-OH D), demographic, social and medical history, and relevant risk factors were obtained. We evaluated serum 25-OH D status and overall PCa risk and tumor aggressiveness (Gleason score 4-9) using Poisson regression and ordinal regression, respectively.

Results: Mean age was 57.4 y/o. PCa family history occurred in 26% of cases and 15% of controls ($p = 0.07$). Mean 25-OH D was 21.4ng/ml in controls vs. 17.0ng/ml in cases ($p = 0.002$) and was 6.3ng/ml higher during the high UV season ($p < 0.001$). After adjusting for relevant covariates on regression, age ($p = 0.004$), family history ($p = 0.047$) and an interaction between season and 25-OH D (< 15ng/ml) ($\beta = 0.68$, $p = 0.032$) best predict PCa. Higher Gleason score was associated with PSA ($p < 0.001$), alcohol use ($p = 0.02$), and the interaction between season and vitamin D < 15ng/ml (OR 9.86, $p = 0.003$).

Conclusion: Among AA men, Vitamin D deficiency in the high UV season increased PCa risk and odds for higher Gleason grade tumors relative to non-deficient men in the low UV season.

Appendix 3: AACR Abstract

Biological and Environmental Correlates of Vitamin D Status in African American and European American Men in Chicago

Murphy AB[2*], Nyame Y[2], Smith DJ[1], Castaneda L[1], Kelley B[2], Minaya K[1], Hollowell CMP[3],

Kittles RA[1].

1. UNIVERSITY OF ILLINOIS AT CHICAGO DEPARTMENT OF MEDICINE, SECTION OF HEMATOLOGY/ONCOLOGY.
2. NORTHWESTERN UNIVERSITY DEPARTMENT OF UROLOGY.
3. JOHN H. STROGER JR HOSPITAL OF COOK COUNTY, DEPARTMENT OF SURGERY, DIVISION OF UROLOGY.
4. * DENOTES CORRESPONDING AUTHOR.

Introduction: Vitamin D deficiency is epidemiologically linked to prostate, breast and colon cancer. African American (AA) men have increased risk relative to European American (EA) men, but few studies evaluate vitamin D status in AA men. We evaluate the biological and environmental predictors of vitamin D deficiency in AA and EA men in Chicago, Illinois, a low ultraviolet radiation (UVR) environment.

Methods: Blood samples were collected from 492 men, age 40-79, from urology clinics at three hospitals in Chicago, along with demographic and medical information, BMI, and skin melanin content using a portable narrow-band reflectometer. Vitamin D intake (dietary and supplemental) and UVR exposure were assessed using validated questionnaires.

Results: Mean and median 25-OH D levels (normal: 30-80 ng/ml) were 17.2 and 16.0 ng/ml in AA men and 26.0 and 25.0 ng/ml in EA men, respectively ($p < 0.01$). Also, 93% of AA vs. 69.7% of EA men (OR = 1.33) were vitamin D deficient ($P < 0.01$). AA status ($p = 0.04$), age, and BMI ($p < 0.01$) were positively correlated with vitamin D deficiency, while vitamin D supplement use and sun exposure were negatively correlated ($p < 0.05$). Our multivariate analysis revealed that AA status, BMI, and lack of vitamin D supplementation were negatively associated with 25-OH D level ($p < 0.05$).

Conclusion: Sunlight exposure, BMI and vitamin D supplementation are associated with vitamin D deficiency and represent modifiable risk factors. Race and sunlight exposure should be taken into account for recommended daily allowances for vitamin D intake.